



Effects of lithium and valproate on oxidative stress and behavioral changes induced by administration of m-AMPH

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ABSTRACT

In the last years our research group has studied and validated the animal model of mania induced by dextroamphetamine (D-AMPH). Considering the lack of animal models of mania reported in the literature; this study evaluated the possibilities to validate the animal model induced by methamphetamine (m-AMPH). Then, we evaluated the effects of lithium (Li), valproate (VPA) on the behavior and parameters of oxidative damage in rat brain after administration of m-AMPH. In the prevention treatment, Wistar rats were pretreated with Li, VPA or saline (Sal) for 14 days, and then, between days 8 and 14, rats were treated with m-AMPH (1, 0.5 or 0.25 mg/kg) or Sal. In the reversal treatment, rats were first given m-AMPH (0.25 mg/kg) or Sal. Locomotor behavior was assessed using the open-field task and parameters of oxidative damage were measured in brain structures. Our results show that the hyperactivity was prevented and reverted by Li and VPA only when m-AMPH was administered in the dose of 0.25 mg/kg. In addition, the m-AMPH in all doses administered induced oxidative damage in both structures tested in two models. Li and VPA reversed and prevented this impairment, however in a way dependent of cerebral area, the dose of m-AMPH and technique.

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1. Introduction

Bipolar disorder (BD) is one of the most severe psychiatric disorders, which is associated with morbidity and mortality and psychiatric comorbidity (Kupfer, 2005; McIntyre et al., 2007). However, despite the severity of the disorder, its pathophysiology remains largely unknown. Animal models are an important tool in gaining insights into the neural mechanisms underlying BD and in assessing potential therapeutic actions of new compounds in preclinical settings (Lipska and Weinberger, 2000; Boksa, 2007). Animal models of human diseases should meet three sets of criteria: face, construct, and predictive validities (Einat et al., 2003; Machado-Vieira et al., 2004). Face validity is the ability of the model to mimic the symptoms of the determinate human disorder, while construct validity is the capacity of the model to mimic some pathophysiological change found in the human disorder. Finally, predictive validity refers to the ability of the conventional drugs used to treat the disorder, prevent and/or reverse the symptoms induced in the model (Machado-Vieira et al., 2004).

Dopamine (DA) is an important neurotransmitter that is involved in cognition, mood and motor functions of the brain (Sibley and Monsma, 1992; Missale et al., 1998). Changes in the dopamine signaling are implicated in numerous neuropsychiatric disorders, including schizophrenia and bipolar disorder (Greengard, 2001). Many of the signs and symptoms of BD can be reproduced in humans and animal models with dopaminergic stimulants such as cocaine and amphetamine. For example, amphetamine (AMPH) administration in rats induces hyperlocomotion, insomnia and increased sexual drive (Fiorino and Phillips, 1999) – symptoms also found in bipolar patients. Additionally, in previous studies, our research group demonstrated that lithium (Li) and valproate (VPA) – two classic drugs for the treatment of BD – reversed and prevented the dextroamphetamine-induced hyperactivity in rats (Frey et al., 2006a,b,c; Andreazza et al., 2008; Valvassori et al., 2010).

AMPHs are psychostimulant drugs of the phenethylamine class that act by increasing DA efflux, inhibit the uptake of DA and inhibit monoamine oxidase (Fischer and Cho, 1979). It is well known that the dopaminergic system and oxidation of DA play pivotal roles in the neurotoxicity produced by AMPHs, which increase the formation of reactive oxygen species (Chipana et al., 2008). Dextroamphetamine (D-AMPH) is chemically related to methamphetamine (m-AMPH), nevertheless, m-AMPH is considered to be a more potent central psychostimulant

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than D-AMPH (Mathias, 1998). However, behavioral and neurochemical differences between D-AMPH and m-AMPH remain poorly understood (Ricaurte et al., 1983; Kuczenski et al., 1995; Shoblock et al., 2003).

Moreover, several lines of evidence show the oxidative damage to lipid and proteins as one of the possible mechanisms contributing to neuronal and glial impairment in BD (Kunz et al., 2008; Andrezza et al., 2010a,b; Steckert et al., 2010). Repeated injections of D-AMPH that induce hyperactivity in rodents is associated with increased in protein and lipid oxidative damage in brain (Gluck et al., 2001; Andrezza et al., 2008; Valvassori et al., 2011), supporting the view that oxidative stress is occurring during a manic-like state. In addition, previous studies of our laboratory also demonstrated that Li and VPA prevented and reversed the D-AMPH-induced oxidative protein and lipid damage in the brain of rats (Frey et al., 2006; Andrezza et al., 2008).

Therapeutic development in bipolar is hampered by a lack of pathophysiological model (Berk et al., 2007). In the last six years our research group has studied and validated the animal model of mania induced by D-AMPH, which has been well accepted in the literature (Frey et al., 2006; Andrezza et al., 2008; Valvassori et al., 2010). Considering: 1) the lack of animal models of mania reported in the literature and 2) the lack of studies showing the difference between D-AMPH and m-AMPH; the present study aims to evaluate the possibilities to validate the animal model induced by m-AMPH. Then, we evaluated the effects of mood stabilizers on the behavior and parameters of oxidative damage in rat brain after administration of m-AMPH.

2. Methods

2.1. Animals

The subjects were adult male Wistar rats (weighting 250–350 g) obtained from our breeding colony. Animals were housed five to a cage with food and water available ad libitum and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.) at a temperature of 22 ± 1 °C. All experimental procedures were performed in accordance with the approval of the local Ethics Committee in the use of animals at the Universidade do Extremo Sul Catarinense. All experiments were performed at the same time during the day to avoid circadian variations.

2.2. Treatment protocols

2.2.1. Prevention treatment

In the prevention model, we simulated the maintenance phase of BD treatment. Animals were treated with Li (47.5 mg/kg i.p.), VPA (200 mg/kg i.p.) or saline twice a day for 14 days. Between the 8th and the 14th days, Li, VPA and saline-treated animals additionally received one daily intraperitoneal injection of either m-AMPH or saline.

From this protocol 3 experiments were made. In experiment 1, a dose of 0.25 mg/kg of m-AMPH was administered and experimental groups were as follows: Sal + Sal, Li + Sal, VPA + Sal, Sal + m-AMPH 0.25 mg/kg, Li + m-AMPH 0.25 mg/kg, VPA + m-AMPH 0.25 mg/kg ($n = 15$ animals per group).

In experiment 2, a dose of 0.5 mg/kg of m-AMPH was administered and experimental groups were as follows: Sal + Sal, Li + Sal, VPA + Sal, Sal + m-AMPH 0.5 mg/kg, Li + m-AMPH 0.5 mg/kg, VPA + m-AMPH 0.5 mg/kg ($n = 15$ animals per group).

In experiment 3, a dose of 0.5 mg/kg of m-AMPH was administered and experimental groups were as follows: Sal + Sal, Li + Sal, VPA + Sal, Sal + m-AMPH 0.5 mg/kg, Li + m-AMPH 0.5 mg/kg, VPA + m-AMPH 0.5 mg/kg ($n = 15$ animals per group).

Locomotor activity was measured 2 h after the last injection. The rats were sacrificed by decapitation immediately after the open-field task and hippocampus, striatum and prefrontal were dissected, rapidly frozen and stored -70 °C until assayed.

2.2.2. Reversal treatment

In the reversal model, we reproduced the treatment of acute manic episode. The animals received one daily intraperitoneal injection (i.p.) of m-AMPH 0.25 mg/kg or saline (Sal) for 14 days. On the 8th day of treatment, the animals in the saline and D-AMPH group were divided in three groups: 1) treatment with Li (47.5 mg/kg i.p.); 2) treatment with VPA (200 mg/kg i.p.) and 3) treatment with Sal for 7 days twice a day for all drugs. On the 15th day of treatment, the animals received a single injection of m-AMPH (0.25 mg/kg) or Sal and locomotor activity was assessed 2 h after the last injection. The experimental groups were as follows: Sal + Sal, Sal + Li, Sal + VPA, m-AMPH 0.25 mg/kg + Sal, m-AMPH 0.25 mg/kg + Li, m-AMPH 0.25 mg/kg + VPA ($n = 12$ animals per group).

The rats were killed by decapitation immediately after the open-field task and prefrontal, amygdala, hippocampus and striatum were dissected, rapidly frozen and

Note: The reversion protocol was made only with the dose of m-AMPH (0.25 mg/kg) in which Li and VPA could prevent the hyperactivity induced by m-AMPH.

2.3. Locomotor activity

Locomotor activity was assessed using the open-field task as previously described (Barros et al., 2002; Frey et al., 2006a,b,c). This task was performed in a 40×60 cm open field surrounded by 50 cm high walls, made of brown plywood, with the floor divided into 12 equal rectangles by black lines. The animals were gently placed on the left rear rectangle, and left free to explore the arena for 5 min. Crossings of the black lines (locomotor activity/horizontal activity) and rearings (exploratory activity/vertical activity) were counted.

2.4. Measurement of oxidative damage markers

Rats treated with m-AMPH or Saline as described above were sacrificed by decapitation 2 h after the last injection and their brains were removed and dissected for evaluation of oxidative damage levels in the prefrontal cortex, amygdala, hippocampus and striatum. Thiobarbituric acid reactive substances (TBARS) and protein carbonyl formation were measured as previously described (Draper and Hadley, 1990; Levine et al., 1994).

Note: For biochemical analysis $n = 5$ animals per group, which were chosen randomly, were used.

2.5. Thiobarbituric acid reactive substances (TBARS)

The formation of TBARS during an acid-heating reaction was measured as an index of ROS production, which is widely adopted as a sensitive method for measurement of lipid peroxidation, as previously described (Draper and Hadley, 1990). Briefly, the samples were mixed with 1 mL of trichloroacetic acid 10% (TCA) and 1 mL of thiobarbituric acid 0.67% (TBA), then heated in a boiling water bath for 15 min. TBARS were determined by the absorbance at 535 nm. Results are expressed as MDA (malondialdehyde) equivalents (nmol/mg protein).

2.6. Measurement of protein carbonyls

The oxidative damage to proteins was assessed by the determination of carbonyl groups based on the reaction with dinitrophenylhydrazine (DNPH) as previously described (Levine et al., 1994). Briefly, proteins were precipitated by the addition of 20% trichloroacetic acid and redissolved in DNPH and the absorbance read at 370 nm.

2.7. Statistic analysis

All analyses were performed with the statistical package for social sciences version 19.0 (SPSS Inc. Chicago, IL, USA). All data are presented as mean + S.E.M. To test differences between groups, we used analysis of variance (ANOVA), followed by Tukey post-hoc tests. In all experiments, P values less than 0.05 were considered to indicate statistical significance.

3. Results

Administration of m-AMPH at 1 mg/kg increased locomotor activity in rats, and both Li and VPA were not able to prevent the hyperactivity induced by m-AMPH (Fig. 1A). Administration of m-AMPH 1 mg/kg significantly increased the carbonyl production (a direct index of cell protein peroxidation) in prefrontal, amygdala, hippocampus and striatum of rats. In addition, Li and VPA were not able to prevent the m-AMPH-induced protein damage in the brain of rats (Fig. 1B). We also found that m-AMPH 1 mg/kg increased lipid peroxidation in all brain structure evaluated – as indicated by increased levels of TBARS. Pretreatment with Li increased and VPA decreased the lipid damage induced by m-AMPH 1 mg/kg in hippocampus. Conversely, Li prevent the m-AMPH-induced lipid damage in the striatum of rats. In prefrontal and amygdala the mood stabilizers were not able to protect against lipid damage induced by m-AMPH 1 mg/kg (Fig. 1C).

Administration of m-AMPH at 0.5 mg/kg increased locomotor activity in rats, and both Li and VPA partially prevent the hyperactivity induced by m-AMPH (Fig. 2A). The administration of m-AMPH 0.5 mg/kg in rats increased the protein damage in all brain structures evaluated, and mood stabilizers were not able to prevent the m-AMPH-induced protein damage in the brain of rats (Fig. 2B). We verified also that administration of m-AMPH 0.5 mg/kg increased TBARS generation in all brain structures evaluated. The pretreatment with VPA significantly diminished AMPH-

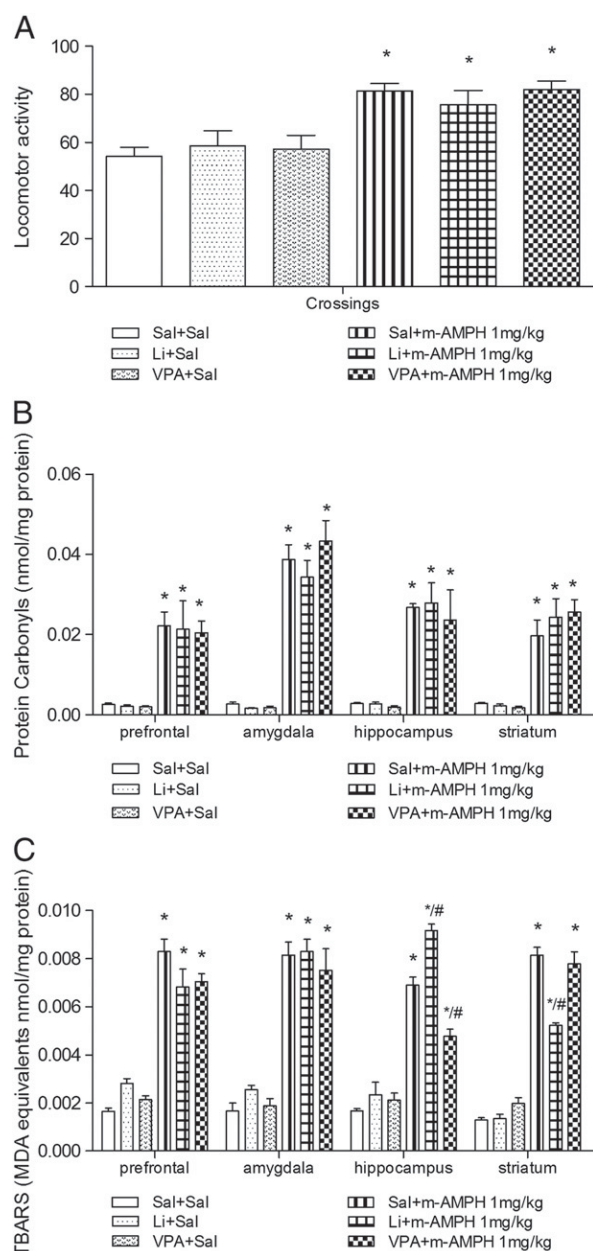


Fig. 1. (A) Number of crossings ($n = 12$ for each group). (B) Protein carbonyl content ($n = 5$ for each group). (C) TBARS content ($n = 5$ for each group) in the prevention model. Rats were pretreated with Li (47.5 mg/kg) or VPA (200 mg/kg) for seven days and then were treated with plus amphetamine until the 14th day of the experiment. Li = lithium, VPA = valproate. Bars represent means; error bars represent standard error of the means (SEM). *Different to the saline group. *# Different to the m-AMPH (1 mg/kg) group.

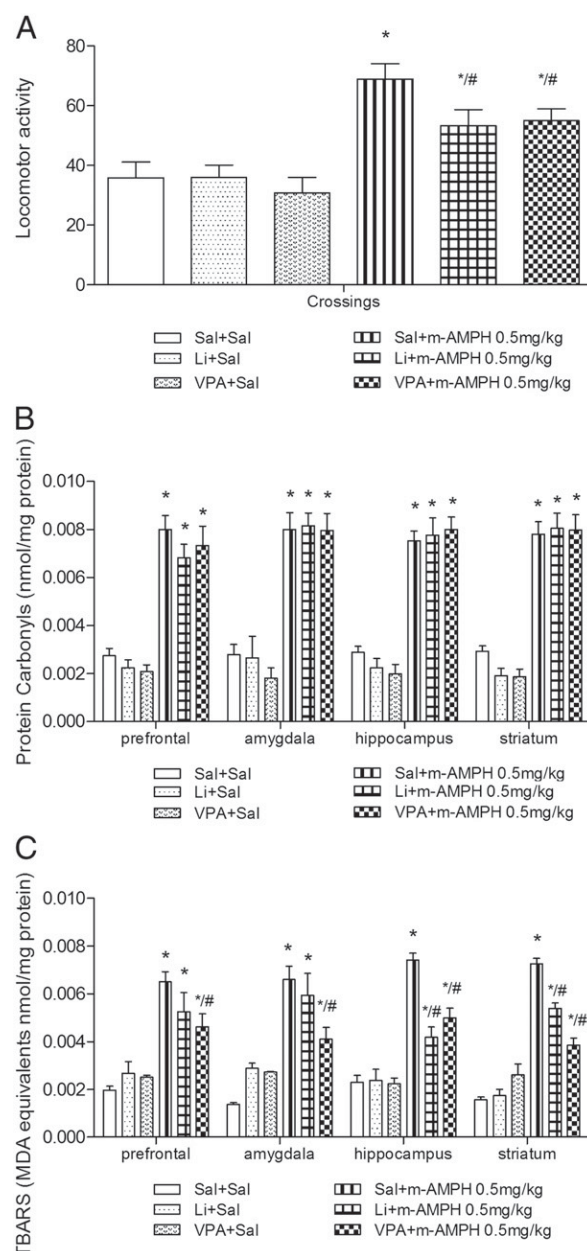


Fig. 2. (A) Number of crossings ($n = 12$ for each group). (B) Protein carbonyl content ($n = 5$ for each group). (C) TBARS content ($n = 5$ for each group) in the prevention model. Rats were pretreated with Li (47.5 mg/kg) or VPA (200 mg/kg) for seven days and then were treated with plus amphetamine until the 14th day of the experiment. Li = lithium, VPA = valproate. Bars represent means; error bars represent standard error of the means (SEM). *Different to the saline group. *# Different to the m-AMPH (0.5 mg/kg) group.

Li partially prevents the lipid damage induced by m-AMPH 0.5 mg/kg in the hippocampus and striatum (Fig. 2C).

Administration of m-AMPH at 0.25 mg/kg increased locomotor activity in rats and both Li and VPA prevented the m-AMPH-induced hyperactivity in rats (Fig. 3A). Besides, the administration of m-AMPH 0.25 mg/kg increased carbonyl group formation in all brain structure evaluated, and both Li and VPA prevented the protein damage induced by m-AMPH 0.25 mg/kg (Fig. 3B). The administration of m-AMPH 0.25 mg/kg increased lipid damage in all brain structures evaluated. Pretreatment with Li protects the brain against lipid damage induced by m-AMPH 0.25 mg/kg in the prefrontal and partially protects the

prevents the m-AMPH-induced lipid damage in the prefrontal, the amygdala and the hippocampus (Fig. 3C).

In the reversion protocol, the administration of m-AMPH 0.25 mg/kg increased locomotor activity in rats and Li and VPA reversed the hyperactivity induced by m-AMPH (Fig. 4A). Once more, the administration of m-AMPH 0.25 mg/kg increased the carbonyl group formation and Li reversed m-AMPH-induced protein damage in all brain structure evaluated. In addition, the treatment with VPA reversed the m-AMPH-induced protein damage (Fig. 4B) in the prefrontal and the hippocampus and partially reversed in the striatum. Besides, m-AMPH 0.25 mg/kg increased lipid damage in all brain structures evaluated. The treatment

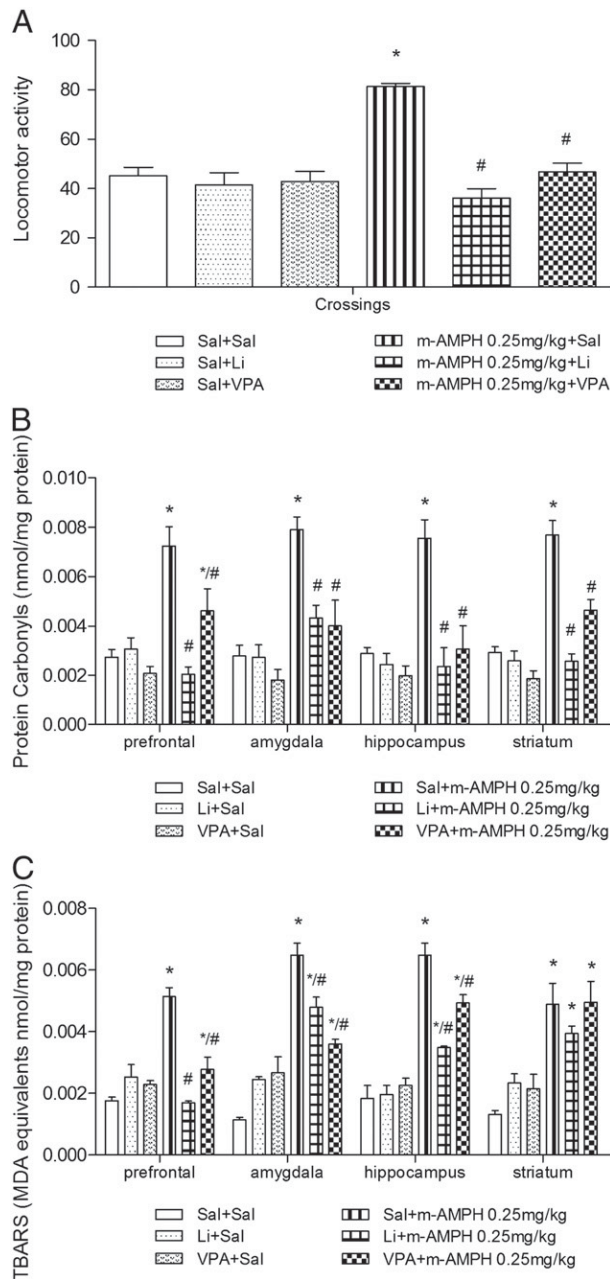


Fig. 3. (A) Number of crossings ($n=12$ for each group). (B) Protein carbonyl content ($n=5$ for each group). (C) TBARS content ($n=5$ for each group) in the prevention model. Rats were pretreated with Li (47.5 mg/kg) or VPA (200 mg/kg) for seven days and then were treated with plus amphetamine between the 8th and 14th days. Li = lithium, VPA = valproate. Bars represent means; error bars represent standard error of the means (SEM). *Different to the saline group. */# Different to the m-AMPH (0.25 mg/kg) group.

in the prefrontal. Moreover, treatment with VPA diminished the m-AMPH-induced lipid damage in the prefrontal and amygdala (Fig. 4C).

4. Discussion

In the present study we observed that all doses of m-AMPH (0.25, 0.5, or 1 mg/kg) increased locomotor activity in rats. However, this hyperactivity was prevented and reverted by mood stabilizers – Li and VPA – only when m-AMPH was administered in the dose of 0.25 mg/kg. In the high doses of m-AMPH, 1 and 0.5 mg/kg, Li and

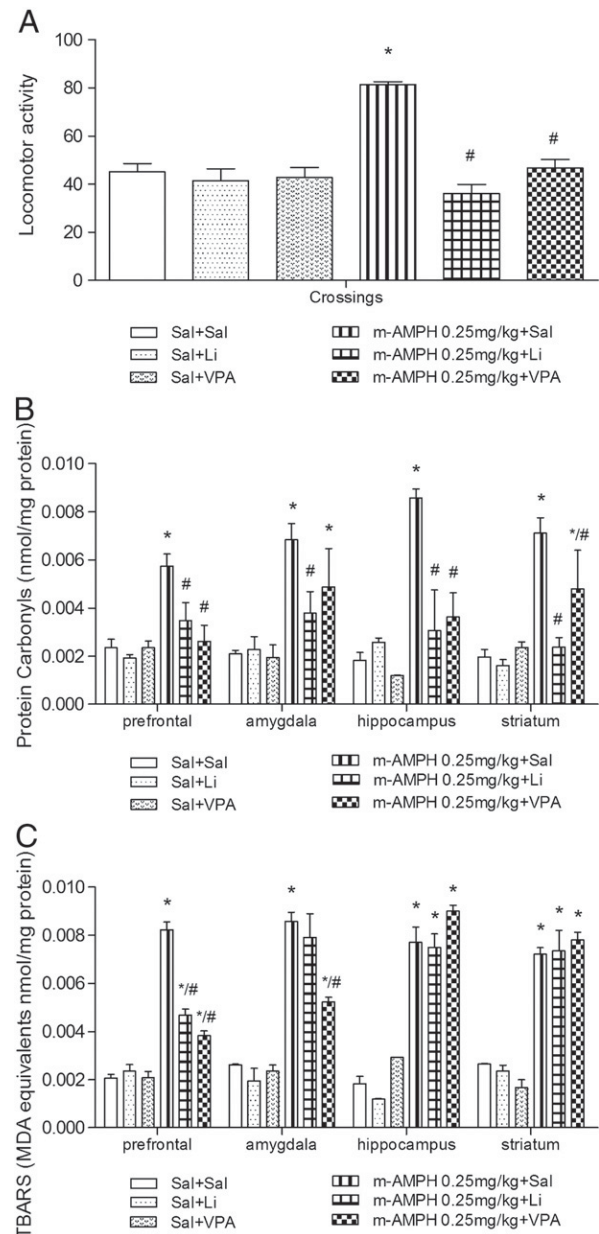


Fig. 4. (A) Number of crossings ($n=12$ for each group). (B) Protein carbonyl content ($n=5$ for each group). (C) TBARS content ($n=5$ for each group) in the reversal model. Rats were pretreated with m-amphetamine for seven days and then treated with amphetamine plus Li (47.5 mg/kg) or VPA (200 mg/kg) between the 8th and 14th days. Li = lithium, VPA = valproate. Bars represent means; error bars represent standard error of the means (SEM). *Different to the saline group. # Different to the m-AMPH (0.25 mg/kg) group.

According to Ellenbroek and Cools (1990) the validity of animal models in psychiatric disorders should demonstrate the face, construct and predictive validities. The clinical hallmark of BD is acute mania (Belmaker, 2004), showing symptoms such as irritable mood, psychomotor activation, reduced need for sleep, and excessive involvement in potentially problematic behavior (El-Mallakh et al., 2003). According to several guidelines or consensus statements, lithium, anticonvulsants such as valproic acid and carbamazepine, and the second generation antipsychotics are recommended for the pharmacological treatment of BD. Here, we demonstrated that m-AMPH 0.25 mg/kg administration increases locomotor activity of rats, and the usual mood stabilizers – Li and VPA – prevents and reverses this hyperactivity in the animals, presenting the face and predictive valid-

It is known that m-AMPH and D-AMPH induces hyperactivity in animals by elevation in extracellular DA (Martinez et al., 2003). There are several studies showing the importance of dopaminergic transmission in the behavioral response to AMPHs. It is well described in the literature that amphetamine dose dependently increases extracellular levels of DA in the brain (Moghaddam and Bunney, 1989; Maisonneuve et al., 1990). Moreover, the blockade of D1 receptors in the medial prefrontal cortex attenuates AMPH- and m-AMPH-induced locomotor activity in the rats (Hall et al., 2009). In addition, intracerebral administration of 6-OHDA, which induces depletion of DA, prevents AMPH-induced hyperactivity (Dunnett et al., 1984; Banks and Gratton, 1995; King and Finlay, 1995) as well as the development of behavioral sensitization following repeated exposure to amphetamine (Bjijou et al., 2002).

Joyce et al. (1995) have found that higher urinary dopamine levels have been associated with the emergence of manic symptoms. In addition, studies have demonstrated dopamine receptor changes in BD patients (Pantazopoulos et al., 2004; Vogel et al., 2004). These studies suggest that the dopaminergic system may play a role in the pathophysiology of BD. In addition, the mechanism of AMPH toxicity has been suggested that involves an increase in the formation of reactive oxygen species (Chipana et al., 2008). It has been widely demonstrated that the generation of reactive oxygen species (ROS) plays a critical role in the pathophysiology of BD (Kunz et al., 2008; Andreatza et al., 2010a,b; Steckert et al., 2010). In the present study we also found that m-AMPH in all doses administrated increased protein and lipid damage in the brain of rats. Finally, the increase in extracellular dopamine together with the oxidative damage induced by m-AMPH, both present in BD, characterizes the construct validity of the model.

Another important result found here is that Li and VPA are not able to prevent protein damage induced by m-AMPH 1 and 0.5 mg/kg. However, when given m-AMPH at 0.25 mg/kg these mood stabilizers prevented and reversed the m-AMPH-induced protein damage. Furthermore, Li increased the lipid damage induced by m-AMPH 1 mg/kg in the prefrontal and VPA partially protects lipid damage only in the hippocampus and striatum. When m-AMPH was administered at 0.5 mg/kg VPA diminished the m-AMPH-induced lipid damage in all brain structures evaluated. However, Li diminished the lipid damage induced by m-AMPH 0.5 mg/kg only in the hippocampus and striatum. Additionally, Li and VPA partially protect against lipid damage induced by m-AMPH 0.25 mg/kg in the prefrontal, amygdala and hippocampus, but not in the striatum. In the reversal protocol, the lipid damage induced by m-AMPH 0.25 mg/kg was diminished by VPA in the prefrontal and amygdala and by Li in the prefrontal. This discrepancy between the prevention and reversion protocols may be due to the fact that the time of treatment with mood stabilizers in the prevention protocol is greater.

In previous studies of our laboratory we demonstrated that D-AMPH increased TBARS levels in the prefrontal cortex, and this effect was reversed by both mood stabilizers — Li and VPA. It was also observed that the administration of Li and VPA increased TBARS formation in the hippocampus of rats pretreated with D-AMPH. In the same study, it has been demonstrated that the VPA pretreatment protects the prefrontal and the hippocampus against D-AMPH-induced lipid damage. However, Li partially prevented D-AMPH-induced lipid peroxidation in the rat hippocampus but augmented in the prefrontal (Frey et al., 2006c). Together, the previous studies and the present study demonstrate that the effect of mood stabilizers depends on the experimental protocol and the brain area analyzed. Regions of the central nervous systems differentially respond to insults (Sullivan et al., 2004) and TBARS formation was evaluated from different brain regions, that in part represent different cell types. Furthermore, within a homogeneous population of cells, there is heterogeneity in terms of physiological and metabolic characteristics (Lai et al., 1977; Sims, 1991; Sonnewald et al., 1998).

It is noteworthy that in the animal model of mania induced by

Here we show that m-AMPH 0.25 mg/kg induces protein damage, which is reversed and prevented by administration of mood stabilizers. In a postmortem study, it was observed that protein oxidation and nitration increased in the prefrontal cortex of bipolar patients (Andreatza et al., 2010a,b). In addition, Andreatza et al. (2009) found a significant increase in 3-nitrotyrosine (marker of protein damage) levels in peripheral blood of patients in the early and late stages of bipolar disorder. From these evidences, we suggest that the animal model of mania induced by m-AMPH is more effective than D-AMPH in mimicking the oxidative brain damage seen in bipolar patients.

5. Conclusions

In conclusion, in the present study we demonstrate that the mood stabilizers Li and VPA reversed and prevented m-AMPH-induced hyperactivity when m-AMPH was administered at 0.25 mg/kg. In addition, the hyperactivity induced by m-AMPH was associated with lipid and protein damage, which Li and VPA were able to reverse and prevent depending on the experimental protocol and the brain region evaluated. Then, we propose a new model of mania induced by m-AMPH, being that this model has face, predictive and construct validities.

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